

Trends, challenges and opportunities in tuberculosis control in rural Ethiopia

Epidemiological and operational studies in a resource-constrained setting

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By

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***To my wife Wengelawit
And children
Loza, Kidus and Ruth***

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Summary

Many people still die of tuberculosis (TB). One-third of the world's population is infected with *M. tuberculosis*, and the poor suffer most. More than 95% of TB cases and deaths are in developing countries and TB is closely linked to poverty. The prevalence of TB increases globally, mainly because of the worsening HIV pandemic. Emerging drug-resistant TB poses another challenge to efforts to control TB. In 1991, the World Health Organization (WHO) introduced a comprehensive approach to TB control, eventually called DOTS- directly observed treatment, short course. Later WHO declared TB a global emergency.

Ethiopia is one of the 22 TB high-burden countries in the world. DOTS was adopted in the first half of 1990s in a few pilot sites, and later expanded. As a result, in 2003, the TB control programme used DOTS in 95% of the public health institutions in the country.

This thesis investigates some elements of DOTS and how these were carried out. The studies focus on epidemiological trends, operational challenges and opportunities to improve TB case finding and treatment outcomes in rural Ethiopia. The aim of the thesis is to assess trend in TB control efforts, estimate the burden of TB, address operational challenges and explore alternative approaches to improve TB case detection and treatment outcomes in rural Ethiopia. The studies were conducted in Hadiya in southern Ethiopia. We used cross-sectional, longitudinal observational and intervention study designs. The studies were conducted in rural communities and in public health institutions. Most of the papers focus on smear-positive TB, the most infectious form of TB.

The study findings show that after five years, the DOTS population coverage reached 75%. Simultaneously, case notification and treatment outcomes of TB patients improved. Between 1994 and 2000, the treatment success for smear-positive TB rose from 38% to 73%. With a decline in treatment failure and default rates, the steadily

increasing trend in treatment success suggests expanding DOTS led to a significant improvement in treatment outcomes.

Trends in case notification and treatment outcomes represent proxy indicators for programme performance. However, to better evaluate the impact of a TB programme, we need both baseline and follow-up data on disease prevalence and incidence. Considering the shortage of resources, we used a simple and less expensive method to estimate the prevalence of smear-positive TB in a rural community. The results show that for every two case of smear-positive TB on anti-TB treatment, there was one undiagnosed infectious case in the community. Such a method of estimating TB burden in a population may bridge the information gap on the extent of TB in resource-constrained settings where case-notification data are incomplete and more sophisticated approaches of estimating incidence and prevalence are not possible.

An intervention study on case finding through a village outreach programme showed the intervention was effective in improving the speed of case detection for smear-positive TB. Though not statistically significant, our study shows a higher case notification rate in the intervention communities compared with the control communities. Patients in both groups had comparable treatment outcomes. This case finding method may be relevant for the new health extension programme in the country that gives due emphasis to community-based approaches. The effectiveness of such an intervention and its cost-effectiveness warrant further investigation.

Improved case detection has a meaning only when the detected cases successfully complete the treatment. This study explored possible causes predicting treatment non-completion among smear-positive pulmonary tuberculosis patients. One in five patients did not complete the treatment and the limiting factor was access to treatment. As most treatment interruption occurred during the continuation phase of TB treatment, clinicians in the TB programme should hold follow-up discussions with patients to ensure treatment compliance in this phase.

Building diagnostic competence is a precondition to improved case finding. Evaluation of routine sputum microscopy for acid-fast bacilli at the diagnostic laboratories over three-year period revealed a declining trend in false readings and 97% overall agreement between the readings at the diagnostic laboratories and that in the reference laboratory. Unfortunately, the number of laboratories taking part in such quality assessment scheme declined, signalling a need to revitalise and scale-up the quality assessment service in the region.

List of original papers

This thesis is based on the following papers, which will be referred to in the text by the respective Roman numerals:

- PAPER I Shargie EB, Lindtjørn B. DOTS improves treatment outcomes and service coverage for tuberculosis in south Ethiopia: a retrospective trend analysis. *BMC Public Health* 2005; 5(1): 62.
- PAPER II Shargie EB, Yassin MA, Lindtjørn B. Prevalence of smear-positive pulmonary tuberculosis in a rural district of Ethiopia. *International Journal of Tuberculosis and Lung Disease* 2006; 10(1): 87-92.
- PAPER III Shargie EB, Mørkve O, Lindtjørn B. Tuberculosis case finding through a village outreach programme in a rural setting in southern Ethiopia: community randomised trial. *Bulletin of the World Health Organization* 2006; 42(2): 112-119.
- PAPER IV Shargie EB, Lindtjørn B. Determinants of treatment adherence among smear-positive pulmonary tuberculosis patients in southern Ethiopia. *PLoS Medicine* 2007 4(2): e37. doi:10.1371/journal.pmed.0040037
- PAPER V Shargie EB, Yassin MA, Lindtjørn B. Quality control of sputum microscopic examinations for Acid Fast Bacilli in Southern Ethiopia. *Ethiopian Journal of Health Development* 2005; 19(2): 104-108.

Acronyms

AFB	Acid-fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ARI	Annual Risk of Infection
BCG	Bacille Calmette-Guérin
CDR	Case detection rate
CI	Confidence interval
CNR	Case notification rate
CSA	Central Statistics Authority
DALY	Disability-adjusted life years
DOTS	Directly observed treatment, short course
EQA	External quality assessment
GNI	Gross national income
HIV	Human Immunodeficiency Virus
ICC	Intra-cluster coefficient
IUATLD	International Union Against Tuberculosis and Lung Disease
LCC	Long course chemotherapy
MDG	Millennium Development Goals
MDR-TB	Multidrug-resistant tuberculosis
MMR	Mass miniature radiography
MOH	Ministry of Health
NPV	Negative predictive value
N TLC P	National tuberculosis and leprosy control programme
PPV	Positive predictive value
PTB	Pulmonary tuberculosis
SCC	Short course chemotherapy
SNNPR	Southern Nations Nationalities and Peoples' Region
SPSS	Statistical package for social science
TB	Tuberculosis
TLC P	Tuberculosis and leprosy control programme
UNICEF	United Nations Children's Fund
WHO	World Health Organization

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1. Introduction

1.1 Tuberculosis: historical outline

Tuberculosis (TB) has claimed countless lives through centuries. Current advances in molecular techniques have enabled the discovery of tuberculosis from mummified remains and bone samples ¹⁻⁵. In line with these findings, some authors have suggested there may be biblical references to TB from the Old Testament books dating to a time when the Israelites lived in Egypt ⁶. Well-documented evidences of large-scale human suffering from this deadly disease, however, date back to the past three centuries. The incidence of TB in Europe and North America increased during the industrial revolution in the 17th and 18th centuries. Since then, there has been a decline in TB prevalence in these countries, mainly because of improved socio-economic conditions ^{7,8}.

Even if TB was recognised during the time of Hippocrates (460-377 BC) as “phthisis” to describe its gradual wasting nature, the origins of TB remained unknown until 1882, when Robert Koch identified the causative agent, *Mycobacterium tuberculosis*. This historic breakthrough was followed by the development of acid-fast stain (AFS) technique in 1885. When Röntgen in 1895 discovered the x-ray, the capacity to diagnose and understand its pulmonary manifestations was improved ⁷. Research during the first half of the 20th century led to the discovery of BCG vaccine in 1921 and two chemotherapeutic agents, streptomycin and para-aminosalicylic acid (PAS) in 1944. More effective treatment and control of the disease using combined chemotherapy ⁸ followed the discovery of Isoniazid and other anti-TB drugs in the 1950s and 1960s .

1.2 Transmission and course of infection

TB is caused mainly by *M. tuberculosis*, and occasionally by other organisms of the *Mycobacterium tuberculosis* complex- *M. bovis*, *M. africanum*, *M. canetti* and rarely, *M. microti* ⁹. The most important source of infection is a person with smear-positive pulmonary TB (PTB). Untreated active smear positive PTB case will infect an average of 10-15 people per year ¹⁰. The tubercle bacilli cannot survive direct sunlight exposure for more than five minutes, but can survive in the dark for long periods ¹¹, which means

that transmission usually occurs indoors. The extent of exposure to the droplet nuclei (duration and dose) and the susceptibility of the host determine an individual's risk of infection¹². *M. bovis* is also transmitted through ingestion of raw-milk containing the bacilli.

Primary infection occurs when a person is newly exposed to tubercle bacilli. Droplet nuclei that are tiny enough to escape the mucocilliary defence of the bronchi, lodge in the terminal alveoli of the lungs and begin to multiply forming a lesion called Ghon focus. The Ghon focus and related hilar lymphadenopathy form a primary complex. Usually the immune response (delayed type hypersensitivity and cellular immunity) controls multiplying bacilli, resulting in a latent infection with a few dormant bacilli. In such cases, the only evidence of infection may be a positive tuberculin skin test. In 5% of the cases, the bacilli overwhelm the immune response and multiply resulting in a primary TB within a few months to a maximum of 5 years¹³. Post-primary TB occurs when the latent infection is reactivated or when the individual is reinfected¹⁴⁻¹⁶. Post-primary TB is characterised by extensive tissue destruction and cavitation, and mainly affects the lungs but can also involve other organs¹¹.

Among infected individuals, the lifetime risk of developing active TB is 5-10%¹⁷. However, the risk may be as high as 50% among immune-compromised individuals such as those infected with HIV¹¹. Among untreated PTB patients, 50% die within 5 years, 25% will be spontaneously cured and 25% will remain with chronic infectious TB.

1.3 Global situation of tuberculosis

It is unfortunate that more than a century after the discovery of the infectious agent and five decades after introducing effective chemotherapy, tuberculosis remains a major cause of death in the world. One-third of the world's population is infected with *M. tuberculosis*, and the socio-economic outcomes of the disease are huge^{10, 11, 17-19}. While the incidence has increased in poor countries, the increase of TB was also noted in some industrialised countries that had successfully lowered its incidence and prevalence²⁰⁻²². In 2000, there were 8.3 million new cases and 1.8 million deaths from TB¹⁹. In 2002,

the figures were estimated to have increased to 8.8 million new cases and over 2 million deaths²². More than 95% of TB cases and deaths are in developing countries where TB accounts for 7% of all and 25% of avoidable adult deaths^{19, 23}. The annual rate of increase in the number of TB cases was 1.8% between 1997 and 2000, whereas the increase was 6.4% in sub-Saharan Africa¹⁹. TB accounts for 2.8% of global disability adjusted life years lost (DALY)¹ in all age groups and 7-8% of all DALYs among those 15-49 years²⁴⁻²⁶. Thus, TB is a major public health concern, ranking 7th as a cause of global DALYs. The unfortunate paradox between the scientific advances in the diagnosis and treatment of the disease and the ever-inclining TB burden is yet to be resolved.

The HIV epidemic has fuelled the TB epidemic in low-income countries. HIV infected people are at increased risk of infection with TB, activation of a latent infection, rapid progression of active disease, and TB deaths^{19, 27-29}. People infected with HIV are 10 times more likely to develop active TB compared to persons not infected with HIV¹¹. Worldwide, 9% of new TB cases in adults and 12% of deaths from TB in 2000 were attributable to HIV. The matching proportions in sub-Saharan Africa were 31% and 39% respectively¹⁹. Although the long-term prospect may be seen with some optimism, the high HIV prevalence makes any TB control effort difficult^{7, 30-35}.

Other conditions leading to TB include immunological factors (chronic illnesses, immuno-suppressive therapy, stress), malnutrition, environmental (overcrowding, repeated and prolonged exposure to TB bacilli), poverty, war, famine and displacement³⁶⁻³⁸. While anyone can get TB, the poor shoulder the greatest burden³⁹. If inequalities in resources and health care provision are not addressed, it is difficult to eliminate TB as a global health threat^{7, 20, 33, 36-39}.

Emerging drug-resistant TB, especially multidrug resistant TB (MDR-TB) poses another challenge of reducing human misery from this deadly disease⁴⁰⁻⁴². In poor areas with many MDR-TB cases, extra cost of second-line drugs is a huge burden to the already underfinanced national TB programmes^{43, 44}. Even if available, these drugs can

¹DALYs from a condition refer to the sum of years of life lost because of premature mortality and years

only be used under close monitoring within a strong TB programme⁴⁵. Efforts have been made by the WHO and its partners to address the issue of “market failures” in getting the drugs, and to strengthen the TB programmes as a condition to tackling MDR-TB^{44, 46, 47}. Despite an encouraging progress, the battle remains far from over⁴⁷⁻⁴⁹.

1.4 Control efforts and targets

Over the past 50 years following the landmark discovery of anti-TB chemotherapeutic agents for combined treatment, the prime question was how the control efforts should be organised. The choice of the control strategy during these years was largely linked to the overall development of health infrastructure especially in the developing world. As a result, the strategy had to switch-off between the specialised vertical and more integrated horizontal approaches, but at large lacked uniformity. In 1991, the World Health Organization (WHO) introduced a comprehensive approach to TB control based on several reports that showed success in dealing with this global scourge in developing set-ups^{17, 50-54}. The approach subsequently took a shape that was widely and enthusiastically accepted and named DOTS- directly observed treatment, short course.

The continuing seriousness of the epidemic in many parts of the world prompted WHO to take an unprecedented step of declaring TB a global emergency. The director of the global TB programme stated that “the growing tuberculosis epidemic is no longer an emergency only for those who care about health, but for those who care about justice”⁵⁵. The declaration was soon followed by the adoption of the DOTS strategy, the WHO-recommended global strategy for TB control. The five pillar elements of the DOTS strategy are: political commitment to national TB control programmes; detection of infectious cases through sputum smear microscopy; standardised case management using short-course chemotherapy under direct supervision at least during the intensive phase; uninterrupted supply of anti TB drugs; and proper registration, record keeping and reporting mechanisms including follow up of treatment outcomes⁵⁶.

of life lived with disability, adjusted for the severity of disability.

Many favour DOTS as one of the most cost-effective of all health interventions^{25, 26, 57}. Global reviews as well as reports from some developing countries also had favourable implications for this strategy⁵⁸⁻⁶⁰. DOTS is equally important in curing TB patients with HIV co-infection and therefore, its importance in the era of the HIV/AIDS epidemic^{61, 62}. Despite its promising prospect, less than 50% of estimated smear-positive TB cases were treated under the DOTS in 2003²².

The global response to the emergency has been scaled up since recently^{63 64}. The aim was to intensify actions to reach the global targets of 70% TB case detection and 85% treatment success for those detected by the year 2005, and to halve the global TB load by the year 2010. The final goal was to remove TB as a global public health problem by the year 2050⁶⁵. To overcome obstacles and strengthen gains in TB control, WHO aims at ensuring proper diagnosis and treatment of all TB patients under programme conditions^{66, 67}. Simultaneously, the two major constraints in the control of TB-TB/HIV^{34, 68, 69} and MDR-TB^{45-47, 70-72}, have been addressed as important elements of the control effort.

Five targets of the millennium development goals (MDG) are concerned with TB. By 2005 the world community aimed to identify 70% of new infectious cases and successfully treat 85% of these cases; by 2015, to have halted and begun to reverse incidence; between 1990 and 2015, to halve TB prevalence and death rates²². However, some of these targets are met with challenges from the outset. For example, case detection under the DOTS in 2003 was reported to be 45% globally, and it might increase to 60% in 2005, 10% lower than the target^{22, 32}. Some fear that it might take nearly a decade after 2005 to reach the 70% target⁷³. Similarly, decline of TB incidence, prevalence and death to the target set for 2015 may hardly be achieved in Africa and probably in Eastern Europe³². Treatment success rates in these regions are at the range of 71-75%, way below the 85% target³². Based on programme conditions, alternative mechanisms for intensified case-finding and increased favourable treatment outcomes should be sought. Decentralisation of DOTS, community-based case finding and treatment, and private-public partnerships in the TB control have shown better results in low-income settings⁷⁴⁻⁸².

2. Tuberculosis in Ethiopia

2.1 *The country*

Ethiopia, one of the oldest civilisations in the world, is also the oldest independent country in Africa. With an area of 1.13 million square kilometres, Ethiopia shares borders with Kenya, Somalia, Djibouti, Eritrea and Sudan. 73 million people live in the country ⁸³, making it the second most populous country in Africa. Over 85% of the population are rural. The major economic base is agriculture that accounts for half of the gross domestic product (GDP) and 80% of total employment. The current annual per capita income is about US\$ 100.

Topographically Ethiopia is divided into the central highland plateau, the rift valley and the coastal lowland areas. The Great Rift Valley that crosses the country from its northeastern border to its southern border with Kenya, divides the high plateau with central mountain range into two. The elevation ranges from 125 metres below sea level at Danakil Depression to 4,620 metres above sea level at mount Ras Dashen. Most of the population lives in the highlands on subsistence farming, whereas pastoralist populations live in the lowlands. The climate is mainly tropical with wide variations and frequent irregularities resulting in repeated periods of drought and famine.

The Ethiopian monarchy ended in 1974 when the military junta set up a socialist state. During 1974-1991, the country operated a central command economy under the military dictatorship. The regime was overthrown in 1991 by the Ethiopian Peoples' Revolutionary Democratic Front (EPRDF). A new constitution was adopted in 1994 and the first multi-party election was held in 1995. Currently, Ethiopia has a federal democratic government with nine ethnic-based regional states and two city administrations, and operates as a market-oriented economy.

2.2 Health care delivery and health-related problems

The health service coverage, defined as part of population living within reach of a health institution in two-hour walking distance, is estimated to be 51%⁸⁴. The major health problems of the country are communicable diseases. Reports suggest the leading causes of outpatient morbidity are malaria, helminthiasis, acute respiratory infections, dysentery, tuberculosis and pneumonia. In 2000, TB was the fifth major cause of morbidity and the second major cause of admissions to hospitals⁸⁴. The estimated HIV prevalence in 2003 was 4.4%, of which 12.6% was urban and 2.6 rural⁸⁵. Table 1 shows some health and demographic indicators.

The current government's health policy aims to improve the access to and quality of health services. Priority is to prevent and control communicable diseases, improve the health infrastructure, develop manpower and strengthen public and private sectors in providing health care^{86, 87}. The government set up a four-tier referral system with a health centre and its five health posts at the base of the pyramid and referral teaching hospitals at the top. To improve access to health care, the government launched a new community-based approach, the health extension package. Under this initiative, well-trained and paid health extension workers live and work within the communities to promote supportive health behaviour and bridge the community health outreach activities.

Table 1: Selected Health-related and demographic indicators for Ethiopia

	Year	Estimate	
		Ethiopia	SNNPRS*
Crude birth rate per 1000	2004	42	44
Crude death rate per 1000	2004	18	18
Annual population growth rate (%)	1992-2002	2.8	2.9
Life expectancy at birth (years)	2002	48	46
Total fertility rate	2002	6.2	5.8
Infant mortality rate per 1000 live births	2000	112	113
Under-5 Mortality rate per 1000 live births	2000	179	191
Maternal Mortality ratio (per 10 ⁵ live births)	2000	850	-
% population using adequate sanitation	2004	6	12
Adult HIV prevalence rate (15-49 years)	2005	4.4	-
Adult literacy rate, per 100	2000	39	-

*Southern Nations, Nationalities and Peoples' Regional State of Ethiopia

Source: UNICEF⁸⁸, WHO⁸⁹ and CSA⁹⁰

2.3 Tuberculosis control efforts

Ethiopia is one of the top 22 TB high-burden countries in the world with an estimated annual incidence of 356 cases per 100,000 ²². The smear-positive PTB incidence is 155/100,000. In 2001, the national TB and leprosy control programme (NTLCP) registered 94,957 TB cases from DOTS areas, representing case notification rates of 173 and 60 per 100,000 population, for all forms of TB and for new-smear positive PTB, respectively ⁹¹. In 2005, a total of 126,233 TB cases were notified to the NTLCP, of which 38,800 (31%) were smear-positive PTB cases. Among adults aged 15-49 years, an estimated 21% of TB cases are HIV-positive, with a great variation among rural and urban areas ranging from 15% to 40% ^{22, 91, 92}.

TB control efforts in Ethiopia date back to the early 1960s, when a few TB centres and sanatoriums were set up in some urban settings. These efforts were not well coordinated until 1976 when the national TB control programme office was established ⁹¹. However, the programme had staff and budgetary constraints. In the early 1990s, the NTLCP was reorganised to strengthen the regional TB programme units and integrate the programme into the general health services. In the meantime, the TB and leprosy programmes were merged to form a single programme.

The DOTS strategy was adopted in the first half of the 1990s in a few pilot sites, and eventually scaled up. In 2003, 95% of the health facilities in the country worked under the DOTS ²². The major partners in carrying out DOTS in the country are the government of Ethiopia, WHO, the Global Fund, the Royal Netherlands Tuberculosis Association (KNCV), the German Leprosy and TB Rehabilitation Association (GLRA) and the US government (USAID and CDC).

2.4 The rationale for the study

The goals of TB control are to reduce morbidity, mortality and transmission and to prevent drug resistance. Well-planned TB control programme may lead to these goals ^{36, 93}. However, TB programmes often suffer from shortage of information necessary for

proper planning and evidence-based decision making. We have limited data from rural Ethiopia on the burden of TB and on what portion of such cases have been detected and effectively treated. Lack of such information makes planning and monitoring of the control efforts difficult. Making scientifically sound baseline information and regularly analysing trends on morbidity, mortality, case-notification, sputum smear-conversion, treatment compliance and diagnostic quality assurance could help to fill the information gap. This study was done to bridge the gap.

TB control efforts relate to the different stages in the pathogenesis and clinical course of TB infection. Figure 1 presents a schematic model of the pathogenesis and clinical course of TB and the study topics covered in the thesis. As discussed earlier, the lifetime risk of developing active TB among infected individuals is one in ten (or more in case of HIV co-infection). Half of undetected and untreated TB cases die within five years, whereas one-fourth gets cured spontaneously and the remaining one-fourth continues to transmit TB to others. Early detection and treatment of cases may alter this course by increasing cure rate, decreasing death and chronic TB, and eventually minimising the extent of infectiousness.

The study examines DOTS in the context of changes in the natural course of TB. Paper-I addresses cross-cutting issues relevant to the different stages of TB: case-detection, registration for treatment, sputum-smear conversion and outcome of treatment. Paper II deals with estimating the load of TB, which in turn, is a reflection of the transmission within a community. Paper III presents an approach that might help to intensify case finding and reduce duration of infectiousness. One of the challenges after case detection is to ensure successful treatment completion. Paper IV looks into the problem of treatment non-completion and its potential determinants. The most feasible diagnostic tool in resource-poor settings for identification of new cases and for monitoring response to treatment is sputum-smear microscopy. Paper V deals with the quality assessment of sputum microscopic examinations at the diagnostic laboratories.

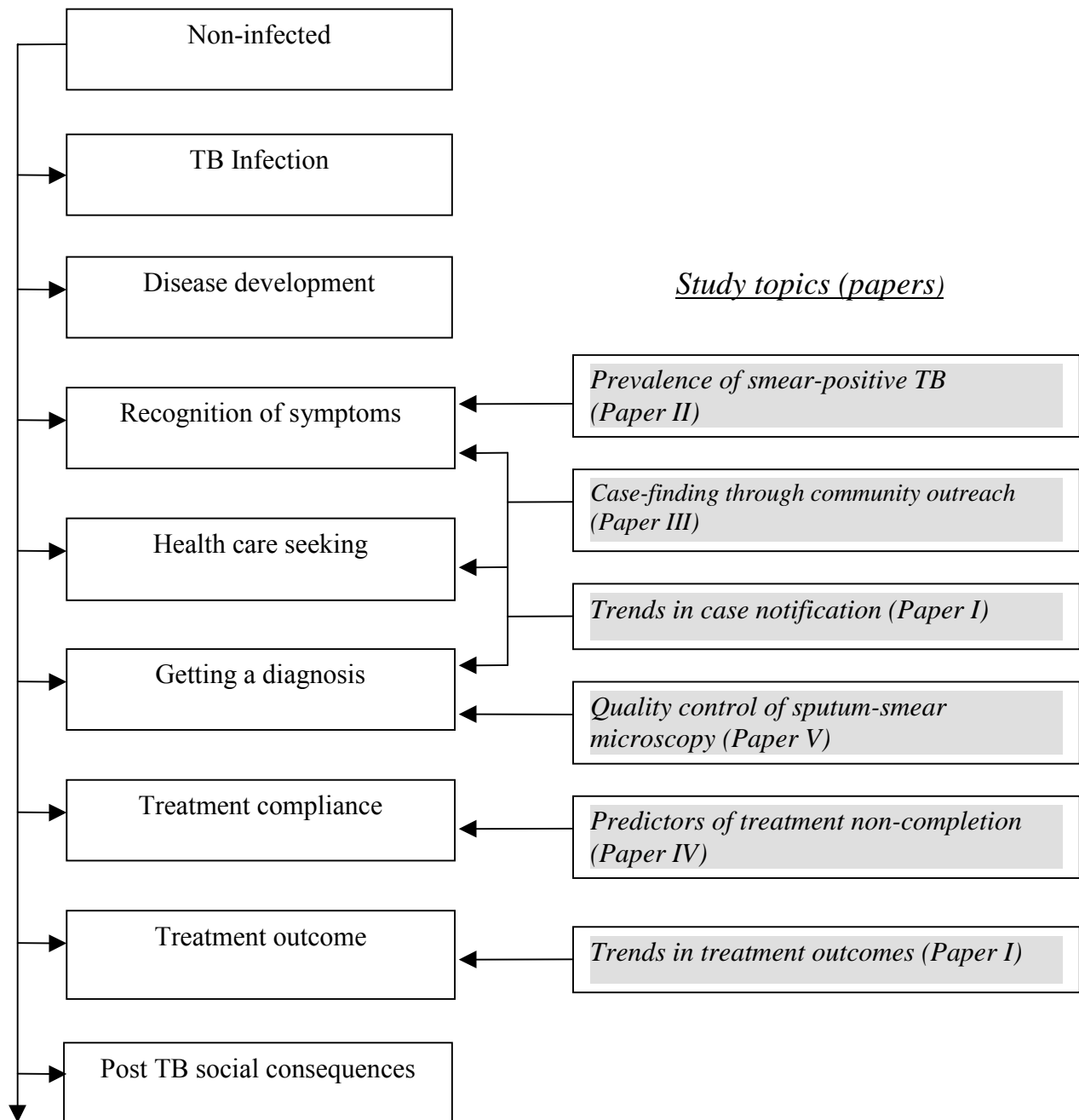


Figure 1: A schematic model of the pathogenesis and clinical course of tuberculosis in relation to the study topics covered in the thesis.

The thesis, therefore, focused on the epidemiological trends, operational challenges and existing opportunities to improve TB case finding and treatment outcomes in rural Ethiopia. Both case detection and treatment success could be influenced by individual, social and biomedical factors⁹⁴⁻⁹⁹. Low case detection may continue to be of concern as most TB programmes remain far short of the global target of 70% case detection¹⁰⁰⁻¹⁰². In the developing world, many TB patients live, transmit and die undetected^{102, 103}, and Ethiopia is not an exception. Low success in treatment completion is another and equally important challenge in most resource-constrained settings. Because of this, there is a need to study the trends in case notification and estimate case detection and treatment success rates (Paper I).

Studies from sub-Saharan Africa report delays in case detection, ranging from 50 to 180 days^{96, 99, 104, 105}. Early detection of cases is key to reduce the duration of infectivity and thus, transmission of the bacilli¹⁰⁶. Intensified case-finding among household members of infectious TB cases is an effective approach in the early detection of cases¹⁰⁷⁻¹⁰⁹. However, in areas with high TB incidence, the main source of infection may be contacts outside the household^{110, 111}. This warrants the need for a broader perspective in improving case-finding and lessening the duration of infectiousness within communities in high incidence settings⁴¹. This thesis tries to address the issue. It tests the value of an alternative community-based approach in improving TB case finding and in shortening pretreatment symptom duration in a setting with low health service coverage (Paper III).

There are few reports on the extent of TB from population-based surveys in Ethiopia. Most of the data come from health institutions, and such data often lack completeness and consistency. In resource-poor settings with low health service coverage, poorly developed diagnostic network and weak disease notification, estimating TB burden from case notifications is difficult. Neither is it possible to oversee the progress in TB control efforts from such data alone. Annual risk of infection (ARI) calculated from tuberculin survey gives a valuable estimate of TB incidence and prevalence¹¹². Another community-based approach for estimating TB prevalence is mass miniature radiography (MMR). However, these approaches are expensive and demand time and expertise. In

this thesis, an alternative approach, screening by symptom inquiry followed by sputum microscopy, is discussed (Paper II).

In resource-constrained settings where the health care services are not well developed, ensuring treatment adherence is another major challenge the TB programmes face ¹¹³. Treatment non-completion may increase the risk of drug resistance, relapse and death and may prolong infectiousness ¹¹⁴⁻¹¹⁶. Before introducing DOTS in Ethiopia, 82% of TB patients failed to complete treatment ¹¹⁷. Though a remarkable decline to 25% was noted after DOTS ¹¹⁸, it is still high. The thesis analyses a 7-year trend in default rate as well as the extent and predictors of treatment non-completion among smear-positive TB patients in rural Ethiopia (Papers I & IV).

This thesis also addresses how the DOTS programmes keep their record and monitor treatment outcomes. Thus, we investigated how complete the TB registers were and how often the TB clinics did follow-up smear examinations (Paper I). The thesis also presents an assessment on the quality control of sputum microscopy in southern Ethiopia (Paper V). Sputum microscopy is the main diagnostic tool for pulmonary TB. External quality assessment (EQA) helps to standardise sputum microscopy for detecting infectious TB in the diagnostic centres and to validate the reported AFB microscopy results from these centres. Evaluating the diagnostic laboratories had not been done and therefore, the need for the current study.

3. Objectives

3.1 *General objective*

The overall aim of the thesis is to assess trend in TB control efforts, address operational challenges and explore alternative approaches to improve TB case detection and treatment outcomes in rural Ethiopia.

3.2 *Specific objectives*

- i. To assess the impact of DOTS expansion on the trends in case notification and treatment outcomes for tuberculosis over time (Paper I).
- ii. To estimate the prevalence of smear-positive pulmonary tuberculosis and burden of undetected TB in a rural community (Paper II).
- iii. To find out whether case-finding through community outreach in a rural setting has an effect on case-notification rate, pretreatment symptom duration, and treatment outcome of smear-positive pulmonary tuberculosis (Paper III).
- iv. To determine factors predicting treatment adherence among smear-positive pulmonary tuberculosis patients (Paper IV).
- v. To evaluate the agreement in the readings of sputum smears for acid-fast bacilli between the diagnostic and reference laboratories (Paper V).

4. Methods

4.1 Description of the study setting

The studies were conducted in the Southern Nations Nationalities and Peoples' Regional State (SNNPRS). It is one of the ten regional states of Ethiopia with a population of 14 million and average population-density of 98 people per square kilometre. The region is unique for its composition of more than 45 indigenous ethnic populations each with its own linguistic and cultural identity. While pastoralist populations live in areas bordering Kenya and Sudan, the majority is settled rural population. The regional TLCP was set up when the national programme was reorganised in 1994. Before setting up the regional TLCP, vertically organised and centrally co-ordinated pilot TB control projects had been carried out in some zones with long- and unsupervised short-course chemotherapy. DOTS was introduced in 1996.

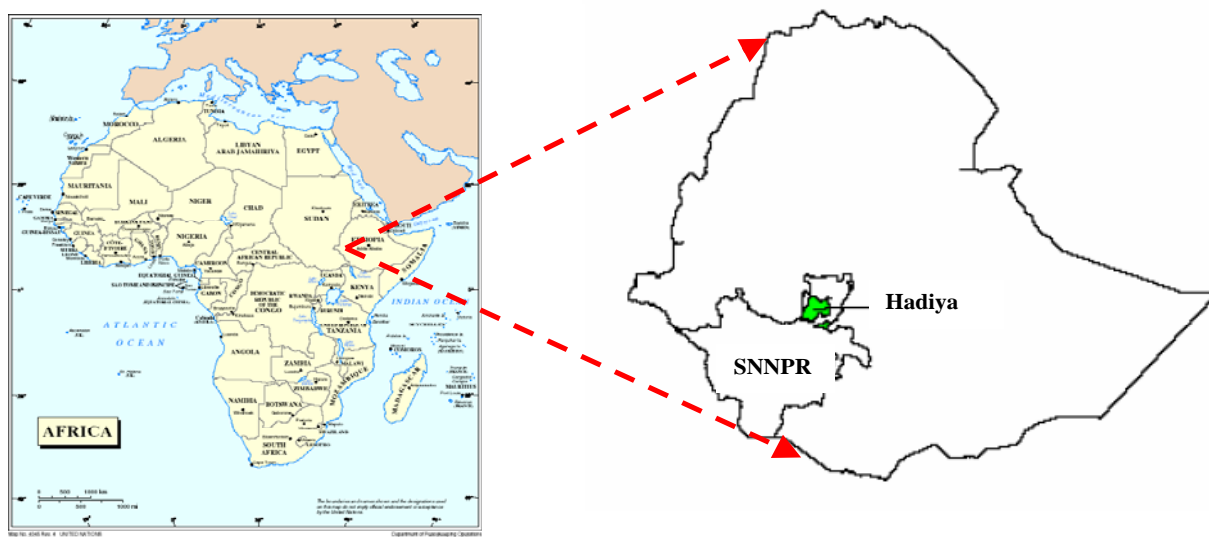


Figure 2: Map of Ethiopia showing the study area.

Data for Papers I-IV are from studies conducted in Hadiya zone (Figure 1), one of the 13 zones in SNNPRS. Paper V is based on data gathered on sputum samples collected from nine zones in the region, including Hadiya, for external quality control. The population of Hadiya is estimated to be 1.3 million ^{119, 120}. Besides 15 TB diagnostic centres including the zonal hospital, five health centres and 21 health stations also provide treatment for TB patients referred or transferred from the diagnostic centres, thus making the number of treatment centres 41. All treatment units provide DOTS and report TB cases to the zonal and regional TLCP.

4.2 Design and data collection

Table 2 summarises the design and the study populations. Detailed study designs and sampling procedures are described in individual papers. Cross-sectional, longitudinal observational and experimental (field trial) study designs were employed. The studies were conducted within rural communities and in public health institutions. Most of the papers study smear-positive PTB.

Table 2: Summary of study designs employed.

Paper	Topic addressed	Design	Study population	Study period
I	DOTS expansion, case notification and treatment outcomes	Retrospective trend analysis	19971 TB patients registered between 1994 and 2001	Jul- Nov 2002
II	Prevalence of smear-positive tuberculosis	Cross-sectional survey	16697 adults surveyed in a rural district	Feb 2003
III	Tuberculosis case finding through a village outreach programme	Community randomised trial	Thirty-two rural communities with a population of 353,000	May 2003-Apr 2004
IV	Predictors of treatment adherence among smear-positive tuberculosis patients	Cohort study	404 smear-positive PTB patients diagnosed in a zonal hospital	Sept 2002-Apr 2004
V	Quality control of sputum microscopic examinations for acid-fast bacilli	Cross-sectional audit	2,209 slides collected from nine zones in SNNPRS	Oct 2000- Jun 2002

In Paper I, we studied 19,971 tuberculosis patients registered for treatment in 41 treatment centres in Hadiya zone between 1994 and 2001. The data were collected from the unit tuberculosis registers. For each patient, we recorded information on demographic characteristics, treatment centre, year of treatment, disease category, treatment given, follow-up and treatment outcomes. We also checked the year when DOTS was introduced to the treatment centre. We analysed the trends in case notification, follow up sputum-smear conversion and treatment outcomes along the course of DOTS decentralisation and expansion.

Paper II employed cross-sectional study design to estimate the prevalence of smear-positive PTB in adults. Using trained data collectors, we interviewed adults older than 14 years by home-to-home visit, and asked for cough of two or more weeks with or without sputum, chest pain or difficulty of breathing. Symptomatic TB suspects gave three sputum samples for standard smear microscopy. The first specimen was collected during the interview, the second early in the following morning, and the third was collected when the data collectors revisited the house. Two experienced senior laboratory technicians examined the sputum smears for acid-fast bacilli (AFB) after standard Ziehl-Neelsen (ZN) hot staining technique¹²¹. As a means of internal quality check, each slide was cross-read twice, by two independent technicians.

Paper III is a community randomised trial. Thirty-two rural communities in two districts of Hadiya zone were randomly allocated to intervention or control groups. The sample size was determined using the formula that considers the coefficient of variation among communities (K), the power of the study, cluster size and the expected outcome¹²². Health workers from seven health centres held monthly diagnostic outreach at 12 intervention communities and got sputum samples from symptomatic tuberculosis suspects for sputum microscopy. Every month, before the outreach day, trained community promoters mobilised house-to-house and at popular gatherings, giving out TB leaflets and discussing symptoms of tuberculosis. Symptomatic individuals were encouraged to visit the outreach team or a nearby health institution. In the control communities, cases were detected through passive case finding among symptomatic

suspects reporting to the health institutions. New smear-positive TB patients living in the intervention and control communities and diagnosed during this period were prospectively enrolled in the study. The outcome measures were case notification rate, pretreatment symptom duration and treatment outcome (success, default, death) ⁹¹. Treatment success was defined as cure (smear-negative at treatment completion and on at least one previous occasion) plus treatment completion without confirmation by smear-microscopy. Default was defined as treatment interruption for more than eight consecutive weeks after a minimum of four weeks on treatment. Treatment failure was defined as remaining or becoming again smear-positive at five months or later during treatment.

The fourth study (Paper IV) used a prospective longitudinal study design to find out predictors of treatment adherence among smear-positive tuberculosis patients diagnosed and registered for treatment in a zonal hospital. Using pretested questionnaire, potential predictor factors for defaulting from treatment were recorded at the beginning of treatment and patients were followed-up until the end of treatment. . Default rate in each stratum of the predictor factors was calculated against total person-time of observation. All defaulters were traced and interviewed regarding the main reason for defaulting from treatment. After the interview each defaulter was encouraged to get back to treatment at the nearest health facility of choice.

The study on quality control of sputum microscopic examinations for AFB (Paper V) is a cross-sectional performance audit. The peripheral laboratories kept all positive slides and an equal number of negative slides (kept at dark places) until the zonal TLCP coordinators collected the needed number of slides. The collected slides were rechecked by microscopists at the regional reference laboratory that were blinded to the readings of the smears at the diagnostic centres. Slides with discordant readings were reread at the central reference laboratory and the readings at the central laboratory were considered as the final result.

4.3 Data analysis and statistics

We used SPSS for windows version 12.0.1 (SPSS inc., Chicago, IL) to analyse the data. Proportions with 95% confidence intervals were used to analyse categorical data. Univariate analysis with Odds ratio and Chi-square tests were used to compare different groups in studies I and IV, and to describe prevalence in study II.

We analysed the data for study III on the basis that all symptomatic TB suspects in the intervention communities intended to use the community outreach services. The unit of randomisation and analysis in this cluster-randomised trial was the community. Weighted means of case detection rate, percentage symptomatic for >3 months, median duration of illness and treatment outcome (success, default, death) were compared using independent sample t-test and Mann-Whitney U test¹²³⁻¹²⁵. The intraclass correlation coefficient (ICC) for each variable was calculated from the one-way ANOVA using the method suggested for estimating ICC from more than one group¹²³ and that for binary outcome variables¹²⁶.

The independent effects of potential predictor variables on the outcome of interest (Adjusted OR, Adjusted HR) were assessed using a logistic regression model (Paper I) and Cox regression model (Paper IV), respectively. Sensitivity, specificity, predictive values, and proportions of false readings were compared using χ^2 test and 95% confidence intervals for proportions in study V. In this study, the agreement among various diagnostic levels was measured using kappa. The statistical significance for all analyses was set at 5%.

4.4 Ethical considerations

The Regional Committee for Medical Research Ethics in Western Norway (REK Vest) and the Ethics Committee of SNNPRS Health Bureau in Ethiopia approved the study protocol. Household heads, TB suspects and PTB patients were interviewed after informed verbal consent was obtained, and the information from each interviewee was kept confidential. Government officials at various levels and community leaders were consulted and permission obtained before the start of field data collection.

5. Main Findings

5.1 DOTS expansion, case notification and treatment outcomes (Paper I)

19971 tuberculosis patients, 11138 (55.8%) males and 8819 (44.2%) females were registered between 1994 and 2001. Forty-six per cent (n=9232) of the patients were smear-positive cases. Overall, 18687 (93.6%) patients were registered as new cases. The proportion of women among registered TB patients remained at the range of 40-45% across the years. The proportion of women among patients older than 45 years was significantly lower (31%; 95%CI 29-33) compared to those below 45 (46%; 95%CI 45-47). Case notification increased from 49/10⁵ population in 1994 to 106 in 1996, 110 in 1998 and 123 in 1999; then declined to 113 and 73 in 2000 and 2001, respectively. The proportion of expected smear-positive incident cases notified increased from 45% in 1994 to 116% in 1999, and declined to 67% in 2001.

The number of health institutions providing DOTS increased from two in 1994 to 10 in 1997, 30 in 1999 and 41 in 2001, raising the population coverage by DOTS to 31%, 58% and 75% respectively. The proportion of patients treated with SCC increased from 7% in 1994 to 27% in 1998, 58% in 1999, and 97% in 2001. Simultaneously, treatment success for new smear-positive TB patients increased from 38% in 1994 to 56% in 1998, 70% in 1999 and 73% in 2000 (χ^2_{trend} , $p<0.001$). Default rate declined from 38% in 1994 to 30% in 1998, 20% in 1999 and 18% in 2000 (χ^2_{trend} , $p<0.001$). Treatment failure decreased from 5% in 1994 to 1% in 2000. The proportion of reported deaths remained unchanged over years with some variations in the range of 2-5%. Patients treated at peripheral treatment centres had higher treatment success and lower default rates compared to the larger ones including the zonal hospital.

5.2 Prevalence of smear-positive pulmonary tuberculosis (Paper II)

This cross-sectional study was conducted with intent to estimate the prevalence of smear-positive pulmonary tuberculosis in a rural setting. Of 16697 adults aged >14 years surveyed by home-to-home visit, 436 (2.6%) were symptomatic and gave sputum

samples for standard microscopy. Thirteen (3%) were positive for acid-fast bacilli, and the prevalence of smear-positive tuberculosis was $78/10^5$ (95% CI 36-120). Twenty-four smear-positive cases identified through the existing health care delivery from the study area were on antituberculosis medication. The ratio of smear-positive cases on treatment to those newly detected by the survey was 2:1 adults suggesting that for every two cases of smear-positive TB on treatment during the survey, there was one case of undetected smear-positive TB in the community. Male to Female (M: F) ratio among patients on treatment was 2.43 (17/7), while that among patients detected by the survey was 0.86 (6/7) (OR= 2.8; 95% CI 0.7-11.5). Patients detected by the survey were younger compared to those on treatment. There was no difference in other socio-demographic characteristics between patients on treatment and those not on treatment.

5.3 Case-finding through community outreach programme (Paper III)

With this study we intended to find out whether case finding through community outreach has an effect on case notification, pre-treatment symptom duration and treatment outcome of smear-positive tuberculosis in a rural setting. We compared these parameters between the intervention and control communities. During one-year period, 159 and 221 cases of smear-positive tuberculosis were detected in the intervention and control groups, respectively. Case notification rates among all age groups in the intervention and control groups were $124.6/10^5$ and $98.1/10^5$ person-years, respectively ($p=0.12$). The corresponding rates among adults aged >14 years were $207/10^5$ and $158/10^5$ person-years ($p=0.09$). Proportion of patients with >3 months symptom duration in the intervention communities was 41% compared with 63% in the control communities ($p<0.001$). Pre-treatment symptom duration in the intervention group showed a 55-60% decline over time compared with 3-20% reduction in the control group. 81% and 75% of patients successfully completed treatment in the intervention and control groups, respectively ($p=0.12$). 16% from the intervention group and 22% from the control group defaulted from treatment ($p=0.11$). One patient in the control group had treatment failure. Death rate was reported to be 3.1% in the intervention group and 3.2% in the control group ($p=0.49$).

5.4 Treatment adherence among smear-positive patients (Paper IV)

This study explored factors predicting treatment adherence among smear-positive PTB patients diagnosed and registered in a zonal hospital. Of 404 new smear-positive PTB patients registered, 43% (n=174) were women. 21% (n=83) of the patients had treatment follow-up at Hossana hospital whereas, 43% (n=169) and 36% (n=139) were treated at the health centres and health stations respectively. 81 (20%) patients defaulted from treatment while 310 (77%) successfully completed treatment. 91% of treatment interruption occurred during the continuation phase. In Cox regression model, controlling for the potential predictor variables, distance from home to treatment centre (HR=2.97; $p<0.001$), age >25 years (HR =1.71; $p=0.02$) and necessity to use public transport to get to treatment centre (HR=1.59; $p=0.06$) remained independent risk factors for defaulting from treatment. It was possible to trace and advise 74 of the 81 defaulters to resume medication. The main reasons given by 45% of the patients for defaulting from treatment were related to physical access (TB clinic too far from home, could not afford transport cost, and too tired to walk to the treatment centre). Mistaken sense of cure, loss of hope in the medication and inadequate knowledge about treatment duration were also among the reasons mentioned by the patients.

5.5 Quality control of sputum microscopic examinations for AFB (Paper V)

With the aim to evaluate the agreement in the readings of sputum smears for AFB between the diagnostic centres and the reference laboratories, 2209 slides, of which 54% were positive and 46% negative, were collected from the peripheral diagnostic centres. The regional laboratory team reread the slides, and 95 of these slides were found to be discordant and sent to the central reference laboratory. Considering the final reading at the central reference laboratory as a gold standard for the true smear result, both the sensitivity and specificity of the peripheral diagnostic laboratories was 96.8%, and the positive and negative predictive values were 97.3% and 96.2 % respectively. While the average false-reading at the peripheral laboratories in the region was 3.2% (range 0-5.1), there was a high degree of agreement (96.8%) between the readings at the peripheral diagnostic laboratories and the final reading ($K = 0.936$, $SE=0.008$). The proportion of false-positive slides declined from 4.4% in 2000 to 2.3% in 2001 and to

1.5% in mid-2002 ($\chi^2_{\text{trend}} = 4.33$; $p = 0.038$). However, there was a no significant reduction of false-negatives: 3.9% in 2000, 2.4 in 2001 and 2.6 in 2002 ($\chi^2_{\text{trend}} = 1.39$; $p = 0.238$). Nine zones took part in the quality control in 2000, six in 2001 and three in 2002.

6. Discussion

6.1 *Methodological considerations*

6.1.1 *Study design and sample size*

This study uses different designs, and each design has its own strengths and limits. The choice of an epidemiological study design depends on the research question under investigation, cost, time and feasibility¹²⁷. Descriptive study designs, such as cross-sectional surveys, do not show temporal relationship between exposure and disease, and one cannot make causal inference from the findings. However, such studies are useful for public health planning, priority setting and resource allocation as they provide valuable information on health status, disease burden and health care needs of a population. Also, the findings may lead to formulating a testable epidemiological hypothesis.

Studies on the prevalence of smear-positive TB (Paper II) and quality control of sputum microscopy for AFB (Paper V) employed cross-sectional study designs. The estimated size of the problem would help evaluating the TB control programme (TB prevalence survey) and the performance of the peripheral laboratories (quality control of sputum microscopy) if repeated at certain intervals. The results would also enable programme managers and clinicians to plan and carry out evidence-based interventions. The descriptive study design may answer the research questions under investigation: What is the prevalence of smear-positive TB? And, what is the level of agreement in the readings of sputum AFB microscopy between the diagnostic centres and the reference laboratories?

We used observational analytic study designs to assess trends in expanding DOTS and treatment outcomes (Paper I), and to find out factors predicting treatment non-completion (Paper IV). Such designs allow simultaneously examining multiple aetiological factors for a single outcome (case-control) or multiple outcomes for a single exposure (cohort). Paper I used several approaches: retrospective cohort analysis (for example treatment outcome between those on SCC vs. those on LCC), case-control

analysis (for example, predictor variables for treatment success and default) and cross-sectional comparison (for example case-notification for men vs. women), and compared the results across the years. The strength of such retrospective study designs depends on the quality and completeness of available data. This particular study was valuable in describing the trend in case-notification, smear-conversion and treatment outcomes over the years. It also described the trends on the expansion of DOTS. Nearly 20% of the patients did not have their outcome record. To increase validity of our results, all patients with missing outcome record were analysed as defaulters, and yet there was an increasing trend in treatment success and decrease in default and failure rates over the years.

To test multiple predictors for treatment, a prospective cohort design was chosen (Paper IV). The prospective design allowed recording of potential risk factors for defaulting from treatment at the beginning of the study. As a result, the risk of recall bias, which is an inherent problem of retrospective study designs, is considered. Also, it reduced time and cost of tracing and interviewing cases and an equal number of controls that successfully completed treatment within the same period. However, this approach has some limits. For example, default rates were not compared in relation to events during treatment such as drug side effects and care provider-patient interactions, which could influence patient's decision to continue treatment. Such factors cannot be recorded at the beginning of the study, and a combined approach may have yielded better results. Overall, and despite inherent limits that I shall discuss later, both case-control and cohort study designs can be used to test epidemiological hypothesis.

Intervention studies are most desirable in epidemiological research as far as issues of cost, feasibility and ethics are sufficiently addressed^{127, 128}. Randomisation distributes all known and unknown baseline factors equally between the intervention and control groups. This makes it easier to compare the groups and enhances validity of the results. Paper III employed a cluster-randomised trial to find out whether case finding through a village outreach programme improved case-notification rate, pretreatment symptom duration and treatment outcome for smear-positive TB. The unit of randomisation was the community since such interventions cannot be allocated to individuals for practical

reasons as well as because of issues related to ethics and “contamination”^{129, 130}. The knowledge of baseline values of the outcome and stratification or matching of the clusters before randomisation based on the baseline values would have added strength to the study. However, the number of clusters included was large enough for unrestricted randomisation, and both groups had comparable baseline characteristics.

Sample size determines the power of a study and thus, the need for adequate sample size to discern a valid statistical association cannot be overemphasised. The papers in this thesis have taken sample size into account in their respective designs. Papers I and V analysed the available data as a whole and the number of patients evaluated was large enough for multiple comparisons. In Paper II, for practical and logistic reasons, we limited our study to eight kebeles (clusters) that were randomly selected, and all households in the selected kebeles were surveyed. In most cluster sample surveys, the number of clusters is expected to be more than this to sufficiently represent the study population. However, the design effect calculated from the study data was 1.04, showing there was no significant inter-cluster variation in the study area. In the community randomised trial (Paper III), the number of clusters needed in each group was determined for the detection of 50% increase in case notification rate in the intervention group. However, the increase after the intervention was 31%, and this increase could not achieve statistical significance ($P=0.09$). An increase in the number of clusters in each wing may have increased the power to detect the effect of the intervention on case notification rate, if it exists. Apart from this, the sample was large enough for the comparison of pretreatment symptom duration and treatment outcome between the groups.

6.1.2 Internal validity

The validity of an epidemiological study is determined by whether the findings reflect the true relationship between the exposure and the outcome. In other words, it is important to find out whether and to what extent alternative explanations such as chance, bias, or confounding accounted for the observed association¹²⁷.

6.1.2.1 Chance

Chance refers to the likelihood that sampling variability (random error) accounted for the observed association. The role of chance is assessed by performing test of statistical significance or by estimating the confidence interval of the effect¹³¹. We addressed the role of chance by performing appropriate statistical tests and estimating the confidence intervals. For example, in the intervention study (Paper III), the ratio of case-notification rate in the intervention group to that in the control group was 31% and the difference in the weighted means between the groups was 47/100,000. However, this estimate lacks precision since the 95% confidence interval of the difference was between -27 and 123. This range crosses the null value (zero) and thus, we cannot exclude chance as a likely explanation for the observed result. The *P* value for this association was 0.09. In epidemiological research, *P* value of less than or equal to 0.05 shows, by convention, the association is statistically significant^{127, 131}. Sampling error could be reduced and precision improved by increasing sample size. As discussed earlier, the precision of the estimated difference in case-notification would have been improved by increasing the study size.

6.1.2.2 Selection bias

Selection bias is a systematic error that occurs when individual subjects are differentially enrolled into the study. In the treatment adherence study (Paper IV), there would be a risk of selecting cases and controls using non-comparable criteria if defaulters and non-defaulters were selected and analysed retrospectively with regard to possible predictor variables. For example, more controls than cases could have been selected from areas near the study hospital, and this could have spuriously overestimated the association between defaulting from treatment and distance to treatment centre. Such bias is unlikely in this cohort study as the potential exposure variables (including distance) were recorded before treatment outcome was known, and the groups were followed over time until they completed treatment, defaulted or otherwise.

In the study on the quality control of sputum microscopy (Paper V), sampling bias in selecting slides for rechecking is potentially unavoidable. Technicians at peripheral

laboratories may keep slides with good quality stains and readings, and this may overestimate the agreement between the readings at the peripheral centres and that in the reference laboratories. Also, diagnostic centres that send slides for external quality assurance are likely to be better performers than those ones that do not send slides for quality check. Therefore, the high agreement between the peripheral and reference laboratories may be an overestimate.

6.1.2.3 Information Bias (misclassification)

Information or observation bias is a systematic error that results when information is differentially obtained from different study groups. Interviewer bias, recall bias and differential misclassification in ascertainment of exposure or disease, are the common forms of information bias. Interviewer bias is of concern in the cohort (Paper IV) and intervention (Paper III) studies that employed interview questionnaires to get information on the potential exposure factors and outcome measures, respectively. In Paper IV, the prospective design of this study has allowed recording of potential risk factors for defaulting from treatment before the outcome was known, and the outcomes were measured not based on interviews. As a result, the risk of both interviewer and recall biases, which are inherent problems of case-control and retrospective cohort study designs, are considered. In Paper III, measurement variation in symptom duration among the interviewers might undermine the true effect of the intervention. To minimise measurement errors, questionnaires were standardised and pretested. Besides, the interviewers received proper training and they were blinded about the expected outcome measures to avoid measurement bias.

Bias because of loss to follow-up is unavoidable in Paper I, where there was no information on treatment outcome for nearly one-fifth of the cohort. Patients with missing information may be different from those for whom treatment outcome was recorded. Analysis of baseline social and demographic characteristics as well as treatment regimen did not show any difference between the groups, however. In line with the WHO/IUATLD recommendations, patients with missing outcome record in our study were all analysed as defaulters. Some of these patients may have been misclassified as defaulters only because of lack of information on their treatment status.

Such non-differential misclassification often dilutes the effect towards the null value. In paper IV, bias due to loss to follow-up was minimal as less than 1% of patients were lost to follow-up due to transfer out.

There is a potential risk of differential misclassification in the study on the quality control of sputum microscopy (Paper V) where the knowledge of readings at the peripheral laboratories may influence the readings at the reference laboratory. Slides read as “positive” may be more vigorously searched for bacilli while those labelled “negative” may not. However, the rechecking in this particular study setting was performed under blinded condition, and the likelihood of such bias is small.

6.1.2.4 Confounding

Confounding is “a mixing of the effect of the exposure under study on the disease with that of a third factor. This third factor must be associated with the exposure and, independent of that exposure, be a risk factor for the disease”¹²⁷. Confounding can overestimate, underestimate or change the direction of the observed association, and must always be accounted for. For example, in the study on TB case finding (Paper III), some areas may have more educated people than other areas and, independent of area of residence, educated people are more likely to seek medical care for their symptoms and to seek care earlier. Also, the incidence of TB may differ from place to place, and independent of place, incidence determines case notification. Such baseline differences need to be accounted for in the design or analysis of epidemiological studies. The papers in this thesis have tried to control for confounding in the design (Paper III) and analysis (Papers IV and I) using randomisation and multivariate analysis, respectively.

6.1.3 External validity

External validity refers to whether the findings of an epidemiological study can be generalised to other populations. This study was conducted in a rural setting in southern Ethiopia that is typical of rural Ethiopia. However, variations in TB prevalence (Papers II & III), TB programme performance (Papers I & V), and treatment adherence (Paper IV) within the country, limits the generalisability of the results. Similarly, as all papers except Paper-I, focused on smear-positive pulmonary TB, we need more studies to find

out whether the findings of for example, predictors of treatment adherence can be applicable to other forms of TB.

6.2 Discussion of main findings

The success of a TB control programme depends on its ability to detect as many cases as possible and successfully treat them, reduce transmission and prevent drug resistance. DOTS is the current global strategy to achieve these goals ⁵⁶. In this study, there was an increase in case notification rate and treatment success, which corresponds with the decentralisation and expansion of DOTS in the area. The regional TLCP began DOTS in the zonal hospital followed by more health institutions every year. Such a gradual scale-up was important in securing the necessary means and in gaining experience to deal with emerging challenges.

Case notification rate (CNR) nearly tripled between 1994 and 1999 and then levelled-off despite an increase in the number of diagnostic and treatment centres. There are two alternative explanations for the increase. The most likely explanation is improved and decentralised diagnostic services resulting in registering large number of backlog cases in the first five years of DOTS. An increase in the incidence of active TB, fuelled by the HIV epidemic, might also explain this trend. Stabilisation in the observed CNR after 1999 may suggest that an increase in case detection has been offset by a decrease in the incidence of active TB.

Meanwhile, there was a promising progress towards the WHO/IUATLD recommended target of 85% treatment success for new smear-positive TB cases. Treatment success nearly doubled between 1994 and 2000 from 38% to 73%. Simultaneously, default rate decreased by more than a half (from 38% to 18%) between the respective years. The trend observed confirms the finding of other studies ^{58, 59} that DOTS works well in resource-constrained settings with low overall health coverage. The scale-up in DOTS fostered increased coverage by SCC, improved access to care through decentralisation of the service and improved patient follow-up, which in turn increased favourable treatment outcome. This implies the challenge of low-case detection and treatment success rates faced by most TB programmes may be overcome if existing opportunities

could be explored and carried out. One such opportunity used in our study setting was decentralisation of diagnostic and treatment services to the existing health services.

On the other hand, this study has identified two key areas of programme weakness. First, improving the record keeping should be a priority as treatment outcomes were not recorded for about one-fifth of the patients. Further, 94% of the patients were registered as new cases, suggesting that some retreatment cases were classified as new. Second, portion of smear-positive TB patients who had follow-up sputa examined for AFB was low, although it has increased over the years. The importance of patient follow-up with sputum examinations cannot be overemphasised in the era with imminent threat of MDR-TB.

The load of TB in a population may be estimated using various methods, each with their strengths and limits. Besides economic analysis of the global burden of disease (for example DALYS), some epidemiological approaches can help to measure the TB problem in a community. In rich countries with well-developed health care institutions, most active cases of TB are detected. Thus, health institution-based case notifications give an accurate estimate of TB incidence. On the other hand, case-notification from health institutions in resource-constrained settings often lacks completeness and consistency because of low health service coverage, inadequate diagnostic network and weak disease notification mechanisms.

ARI calculated from tuberculin surveys, is another epidemiological tool useful in estimating the TB incidence and prevalence¹³². Prevalence of active TB may also be estimated using mass miniature radiography (MMR) followed by sputum microscopy¹³³⁻¹³⁵. Both approaches are effective, but financial constraints and demand for expertise limit their use in poor countries. In Ethiopia, the last tuberculin survey was conducted fifteen years ago¹³⁶. Alternative approaches are therefore critical for estimating the prevalence and to oversee progress in TB control efforts.

This study estimated the prevalence of smear-positive pulmonary TB in a rural district using symptom inquiry followed by sputum microscopy for AFB. The results show that

for every two cases of confirmed smear-positive TB on treatment, there was one case of undetected infectious TB in the community. Though the prevalence was lower than expected ¹³⁷, it was higher than that reported from other African countries ¹⁰³. In addition, more men were identified before the survey and were on treatment, whereas the ratio of men to women was similar in the survey. Besides the possibility of real gender difference in TB epidemiology ¹³⁸⁻¹⁴⁰, this finding suggests possible existence of gender differentials in access to health care, access by women being less ^{141, 142}.

Estimating TB prevalence using symptom inquiry and sputum microscopy is a simple and cheap technique. Such a method could bridge the information gap on the size of TB in resource-constrained settings. However, this method has some limits. It would only identify cases that report their symptoms. In addition, because of atypical clinical manifestations among HIV co-infected patients, some may not report their symptoms and, even if they report, the chance of smear-positivity is lower. As a result, this method should be considered only when studies with more accurate results, like tuberculin surveys and combined MMR with symptom inquiry and sputum microscopy are technically or logistically impossible. Under such circumstances, use of clinical algorithm with sputum microscopy may help to improve this tool to better estimate TB prevalence.

The NTLCP manual for laboratory technicians recommends rechecking of a sample of routine slides to ensure the quality of sputum microscopy in the diagnostic centres ¹⁴³. Rechecking of routine slides could be used interchangeably or with proficiency testing-monitoring of microscopists by sending centrally prepared panel of stained smears to peripheral laboratories. Although the former is more laborious, it represents the routine performance ¹⁴⁴. This study was based on routine rechecking, and documented a good agreement between readings in the peripheral laboratories and that in the reference laboratories. Further, the extent of false readings declined over three-year period. Unfortunately, many diagnostic centres were not involved in the EQA and further, the number of zones and health institutions taking part in the programme decreased from year to year. It is unclear how those laboratories that do not send slides for quality-check perform. As a result, the study findings might not represent the overall

performance in the region. Revitalising the quality assurance within the region should be a priority.

With our study design, it was not possible to estimate the exact degree of discordance between the diagnostic and reference laboratories, as quantification was not part of this exercise. The NTLCP has recently changed the guideline to include quantification as part of sputum microscopy⁹¹. Nevertheless, quantification does not have implications for case management. As far as patient management is considered, the finding of 97% agreement between the peripheral and final readings is encouraging. However, the 3.2% false-positive reading is too high and warrants further intervention. Expansion of the quality control scheme to all peripheral laboratories with regular supervisory visits, provision of timely feedback and regular refresher training programmes are issues for consideration.

Case finding is one of the major challenges in TB control^{100, 101}. The current WHO and IUATLD guidelines underline case finding through sputum microscopy among symptomatic TB suspects reporting to health institutions⁶⁶. However, individual, socio-cultural, biomedical and environment reasons could influence case finding. Improved diagnostic setting and procedures play an important role in case finding. Such efforts yield better results only if complemented by mechanisms to improve access to these services by the patient. Further, many patients in rural settings present to diagnostic and treatment centres long after the active disease has occurred^{96, 99, 104, 145}. This study sought to test an alternative approach to case finding- case finding through a village outreach programme. The findings show the intervention improved the speed, but not the extent of case detection for smear-positive TB.

As some patients with active TB may not report to the diagnostic and treatment services, we should consider new approaches for active case finding. The approaches for active case finding include MMR, periodic symptomatic case screening and household contact screening. Periodic symptomatic case screening and MMR for active case-finding were reported to be less effective than expected in middle- and high-

income settings¹⁴⁶⁻¹⁵⁰. One of the arguments was that many infected individuals develop active disease before the next screening. Further, it has been concluded that 90% of smear positive TB cases present with symptoms and most seek treatment from health services¹⁵¹. This assertion may not hold true for resource-constrained settings where studies show that many smear-positive TB cases had not been on treatment^{137, 152-156}. Yet, there appears to be no consensus on the role of active case finding in low-income settings. Many disparaged it because of increased workload on the health services and cost implications, while others believe that it is cost-effective in countries with high prevalence, low case detection and moderate to high treatment completion¹⁵⁷. Nevertheless, many agree that current case detection rates are inadequate and need to be improved^{100, 101}.

This study was conducted in a typical rural setting. Though most smear-positive TB patients sought medical care from a public health service at a certain point during their illness, there was a long delay before diagnosis and treatment. Half of the population would have to travel more than two hours to get care in a public health institution. Private clinics are nearly non-existent, and delays in diagnosis and treatment occur while seeking care from alternative health care providers such as traditional healers. To increase basic health service coverage by reducing the access gap, the government has recently embarked on an initiative called “health service extension package”. This package caters for a community-based approach. Thousands of health extension agents have been identified and trained since recently. These new front-line cadres of health might play an excellent role in improving TB case-finding and case-holding under the DOTS programme.

TB treatment aims to cure the patient and eventually break transmission of the bacilli. In this mainly rural setting, one-fifth of the registered smear-positive TB cases failed to complete treatment. Only half of the population live within reach of a health institution in two-hour walking distance¹⁵⁸, and 72% of patients in our study cohort came from within this circle. Among patients that came from areas outside this circle, half of them failed to complete treatment. As such, the main predictors of treatment non-completion

relate to physical access to treatment centre. Most patients interrupted treatment during the continuation phase.

Defaulting from treatment is required to fall below 10% to achieve treatment success of 85%, one of the health related indicators of the millennium development goals ²². Decentralisation of treatment follow-up to community health posts and improved patient-provider communication may reduce the extent of this problem.

6.3 Implications of the study findings

TB programme managers, policy makers and researchers need to analyse trends, challenges and opportunities on the ground to design proper interventions within a local context. Some of the challenges that this thesis identified include many patients with undiagnosed TB, long delay in diagnosis, deficiencies in diagnostic quality control, high rate of treatment non-completion and incomplete recording of treatment outcomes. Decentralised care under the DOTS programme, community-based approaches for case detection and case holding, and a policy environment that fosters community-based health extension programme are among the opportunities to be explored further.

Trend analysis is important in finding out the burden of TB and how good the control efforts are. Therefore, it should be an integral part of programme planning and evaluation. Our study further showed improved case finding and reduced diagnostic delay in diagnosis of infectious TB cases through a community outreach programme. Therefore, managers and policy makers should consider community-based TB case finding as one of the ingredients of the health extension package. Such initiatives may yield better results if complemented by continuous quality assessment and improvement of diagnostic services. As part of improving case detection rate, external quality assessment of AFB microscopy should be made a compulsory exercise in all diagnostic laboratories.

It has been encouraging to note increasing treatment success, mainly because of decline in default rate. However, treatment success was 74% and less than the 85% target. Further, treatment non-completion was high. The main cause influencing treatment

completion was availability of treatment centre. I recommend decentralising TB treatment to community health posts. Such move should also include training on record keeping, distinguishing between new and retreatment cases and follow-up sputum microscopy.

6.4 Areas for further research

There is scarcity of population-based data on the prevalence and incidence of TB in Ethiopia. Fifteen years have passed since the nation-wide tuberculin survey was done and the TB epidemiology may have changed since then. A simple technique of symptom inquiry and sputum microscopy used in this study should be refined and improved.

The study on case finding through village outreach programme proved to be successful in reducing pretreatment symptom duration. However, despite a notable effect size, the difference in case notification between intervention and control groups was not statistically significant. Larger studies in multiple settings should be conducted. It is advisable that such studies also include cost-effectiveness analysis and baseline case notification rates to measure an independent effect of the intervention.

For treatment adherence, a design that combines recording of potential predictor factors at the beginning and retrospective recording of events during treatment may help to understand the interplay of reasons that determine treatment adherence. Future research in this area should also explore the role of such interventions as decentralisation of treatment follow-up to community health posts and improved patient-provider communication. Peer-encouragement mechanisms such as forming “TB clubs”^{82, 159} have shown promising results, and may be worth testing at a broader scale.

Unfortunately, we were not allowed to screen patients for HIV. Therefore, it was not possible to find out the effect of HIV on case notification rate (Paper III) and treatment compliance (Papers III & IV). In Paper IV, less than half of the patients volunteered for

HIV screening, and as a result, we were not able to find out how much HIV status influenced treatment interruption in our study setting. Future studies may yield better results if the data are disaggregated by HIV status.

7. Conclusions and recommendations

This thesis addresses some important areas in tuberculosis control in resource-limited settings. Trends in case notification and treatment outcomes were assessed. These parameters represent proxy indicators for programme performance and may be used to oversee TB control efforts. Further, considering the shortage of resources in many developing settings, a simple method to estimate the prevalence of smear-positive TB is recommended.

The results of routine quality-check of AFB microscopy showed a promising trend that need to be strengthened. Unfortunately, the study showed that many laboratories are not taking part in the EQA of AFB microscopy, which suggests a need for revitalising this initiative.

A community randomised trial on case finding through a village outreach programme proved to be successful in reducing diagnostic delay and it may improve case detection. Such intervention may easily be carried out with the new health extension package.

In this study, some TB registers contained incomplete data. And, treatment follow-up with sputum microscopy was not done for more than one-third of smear-positive TB patients. Further, nearly one-fifth of the infectious TB cases interrupted treatment.

Based on these conclusions I suggest the following recommendations:

Recommendations for research:

- Data for the analysis of trends in TB case detection or notification, and treatment outcomes could easily be obtained from unit or district registers; such data should be used to evaluate how existing control programme has been performing.

- Symptom inquiry plus sputum AFB microscopy may serve as an alternative tool for estimating prevalence of smear-positive TB, especially for programme impact evaluation purposes in resource-constrained set-ups.
- Approaches to intensify case finding such as that through village outreach programmes may speed up the detection of infectious cases and should be evaluated in a broader scale.
- Interventions to improve treatment adherence, such as decentralisation of treatment follow-up to community health posts, improved patient-provider communication and peer-encouragement mechanisms like TB clubs should be explored further.
- Besides EQA of sputum AFB microscopy through rechecking of routine slides, periodic proficiency testing might help in assessing the microscopists in the diagnostic laboratories.

Operational recommendations:

- TB programme staff should receive proper training on case classification, treatment monitoring, record keeping and outcome recording.
- Follow-up sputum microscopy should be strengthened to monitor patient progress for all smear-positive cases under treatment because of the risk of MDR-TB.
- Diagnostic laboratories should keep and send slides for EQA of sputum smear microscopy. As such, continuous on the job training of laboratory staff is important to improve the diagnostic capacity.
- Health promotion activities need to be an integral component of TB case finding and case holding plans.

Policy recommendations:

- Decentralising TB case finding and treatment to health posts may improve case notification and treatment compliance.
- Community-based TB case finding should be one of the major components of the health extension package.
- The quality control scheme for sputum AFB microscopy should involve all diagnostic laboratories and be supplemented by proficiency testing.
- Evaluating the TB programme should involve not only assessing trends in case notification and treatment outcomes but also estimating trends on disease prevalence and incidence using simple methods.

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Original papers (I-V)

